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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#17

APPLICANT: Anaquest, Inc.

U.S. PATENT NO. 4,762,856 **DATE:** NOV. 16, 1992

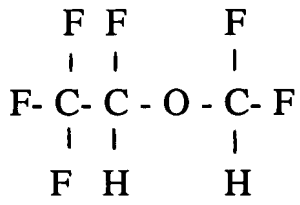
ISSUE: August 9, 1988

APPLICATION FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. §156

The Commissioner of
Patent and Trademarks
Box Patent Extension
Washington, D. C. 20231

Anaquest, Inc. (hereinafter "Applicant") hereby petitions for extension of the above-noted United States Patent pursuant to 35 U.S.C.§156 and states in part thereof as follows:

(1) The United States Food and Drug Administration (FDA) has approved a New Drug Application (NDA) for a human drug product, i.e., Suprane™ (desflurane) liquid inhalation anesthetic (hereinafter "Product") which is effective and useful for anesthetizing by inhalation. The chemical name of desflurane is 2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane, which has the following structure:



(2) The applicable Federal statute under which the regulatory review occurred for the Product is Section 505 of the Food, Drug and Cosmetic Act (FDC Act) (21 U.S.C. §355).

(3) The Product received permission from the FDA for commercial marketing and use under Section 505 of the FDC Act on September 18, 1992.

(4) The Product was not previously approved by FDA.

(5) This Application is being submitted before November 17, 1992, that is within the sixty day period after approval that is permitted for submission of the Application.

(6) The patent for which an extension is being sought is U.S. Patent No. 4,762,856, which was issued August 9, 1988 in the name of Ross C. Terrell and which was assigned to BOC, Inc. of Montvale, New Jersey, who, in turn, assigned the patent to Anaquest, Inc. (a wholly-owned subsidiary of BOC Health Care, Inc.). Anaquest, Inc. the Applicant, has been given authority to act on behalf of this patent. The assignments are included as Attachment 1.

(7) A copy of this patent is attached hereto (Attachment 2).

(8) There are no disclaimers, certificates of correction or reexamination certificates and no maintenance fee is due and payable for this patent.

(9) U.S. Patent No. 4,762,856 claims a method of using the Product. The patent has the following claim:

> A method of inducing anesthesia in a warm blooded animal comprising administering by inhalation to said warm blooded animal an anesthesia inducing effective amount of 2-(difluoromethoxy)-1,1,1,2-tetrafluoroethane as an inhalation anesthetic while administering a life supporting amount of oxygen.

This claim reads on the approved product in that the FDA has approved the Product for the following indication:

> Suprane™ (desflurane) is indicated as an inhalation agent for induction and/or maintenance of anesthesia for inpatient and outpatient surgery for adults.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) needed to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

The Investigational New Drug (IND) Application for the Product became effective on December 21, 1988, IND No. 32,363.

The New Drug Application (NDA), NDA No. 20-118, was initially submitted to the FDA on January 30, 1991.

The NDA was approved on September 18, 1992.

Accordingly, the "regulatory review period" pursuant to 35 U.S.C. §156 is equal to the sum of the IND period, 770 days, and the NDA period, 598 days, which is a total of 1368 days.

(11) A brief description of the significant activities undertaken by the Applicant during the applicable regulatory review period with respect to the Product are as follows:

SUPRANE™ (desflurane) IND 32,363	
DATE	
11/17/88	Submitted IND to FDA
12/1/88	Received acknowledgement of submission and assignment of IND #32,363
1/4/89	Submitted protocol amendment for protocol 04
1/26/89	Submitted protocol amendment providing for change in protocol 02 and the addition of a new subinvestigator
2/2/89	Submitted clinical information amendment which contained revised case report form for protocol 04
2/8/89	Submitted protocol amendment for change in protocol 02 to change patient inclusion criteria
2/21/89	Submitted protocol amendment for the addition of protocol 03
3/10/89	Submitted protocol amendment for change in protocol 04
3/28/89	Submitted information amendment for the revision of the Specifications and Directions for Testing I-653
3/28/89	Submitted protocol amendment for change in protocol 02 allowing for flexibility in the times of urine specimen collection and other laboratory tests
4/5/89	Submitted protocol amendment for protocol 05A
4/7/89	Submitted protocol amendment for protocol 05B and change in protocol 03 to clarify several protocol points
4/28/89	Submitted information amendment for new pharm/tox and clinical information
5/2/89	Submitted protocol amendment adding new protocols 05C, 06A, and 06B
5/17/89	Submitted protocol amendment adding investigators to 06A and 06B and revised case report forms for 03, 04, and 05
6/6/89	Submitted general correspondence informing FDA that desflurane has been accepted as the USAN name for I-653
6/13/89	Submitted protocol amendment adding new investigators to 05B, 05C, and 06A as well as changes to protocols 05B and 06B

SUPRANE™ (desflurane)
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DATE	
6/14/89	Submitted protocol amendment for new protocol 05D
6/26/89	Submitted protocol amendment for new protocol 06C
7/21/89	Submitted protocol amendment for changes to 05A and 05D
8/10/89	Submitted protocol amendment for new protocol 07
9/14/89	Submitted information amendment providing for 1) review in summary form of results of Phase I and II clinical studies to date, 2) proposed Phase III clinical plan, 3) updated investigator brochure, and 4) an overview of special pharmacology studies for discussion at 9/27/89 meeting at FDA
9/22/89	Submitted protocol amendment for new protocol 09A and revised investigator brochure
10/11/89	Submitted protocol amendment for new protocol 10A and new investigator information for 05B, 05C, and 06A
10/26/89	Submitted protocol amendment providing for increased number of patients to be enrolled in study 02
10/31/89	Submitted protocol amendment for new protocol 09C
11/20/89	Submitted protocol amendment for new protocol 09B
11/21/89	Submitted protocol amendment providing new investigators for study 07, and change to 07
11/21/89	Submitted protocol amendment for new protocol 08A
11/29/89	Submitted protocol amendment for new investigators to studies 05C, 07, 09A, and 09C
12/1/89	Submitted protocol amendment for new study 08B
12/5/89	Submitted protocol amendment for new study 10B
12/20/89	Submitted information amendment for new manufacturing site, change in packaging from 250 mL to 240 mL and revised package labeling
1/2/90	Submitted protocol amendment for new protocols 10E and 10F and new investigator information for 09A and 09B
1/15/90	Submitted protocol amendment for new protocol 10H
1/22/90	Submitted protocol amendment for new investigator to protocol 10H

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DATE	
1/24/90	Submitted protocol amendment for new protocols 10G and 10I
1/29/90	Submitted protocol to provide for changes to 02, 05B, 06C and 09B and for new protocols 11 and 12A
2/1/90	Submitted protocol amendment for changes in protocols 05A, 05B, 05C and 10A; new investigator information for protocols 05A, 05C and 11; and new protocol 12B
2/7/90	Submitted protocol amendment for changes in protocols 06A, 09A, and 09C and new investigator information for protocol 10E
2/7/90	Submitted information amendment
2/9/90	Submitted protocol amendment for new protocol 10D and new investigator information for 11
2/16/90	Submitted protocol amendment for new protocol 10C and new investigator and replacement page for protocol 11
2/21/90	Submitted protocol amendment for new investigator information for 10E
2/27/90	Submitted protocol amendment for change to 06B and 10E and new investigator information to 11
3/8/90	Submitted protocol amendment for change to 10F and new investigator information for 10F
3/13/90	Submitted protocol amendment for change in protocols 09A, 09C and 11; new investigator information for protocols 10C and 11; and a revised CRF for 10E
3/19/90	Submitted protocol amendment for changes in 05A, 10G and 11 and new investigator information for 10G
3/23/90	Submitted annual report for the time period 11/88-11/89
4/4/90	Submitted protocol amendment for changes in 10B and 10F and new investigator information for 09C
4/17/90	Submitted protocol amendment for new investigators for 09D and 10K and change to protocol 09D
4/19/90	Submitted protocol amendment for change to 07, 10D and 10H and new investigator information for protocols 10D and 12B
4/24/90	Submitted protocol amendment for new investigator to 10J and 12B

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DATE	
5/3/90	Submitted protocol amendment for change to 09A, new protocol 07A, and investigator information for 10K
5/11/90	Submitted changes to 09B and 12B and new investigator information for 10G
5/16/90	Submitted changes to 10A and 11 and new investigator information for 09C and 10G
5/24/90	Submitted change to 10E and new investigator information for 09B
5/30/90	Submitted change to 10D and new investigator information for 11
6/4/90	Submitted information amendment for four preclinical study reports
6/7/90	Submitted change to protocols 09B, 10D, 10F and 10G and new investigator information for protocol 10E
6/8/90	Submitted information amendment
6/11/90	Submitted new investigator information for 12B
6/15/90	Submitted change to protocol 12B
6/20/90	Submitted change to protocol 09A and new investigator information to 09B and 10C
7/3/90	Submitted change to protocol 11
7/17/90	Submitted change to protocols 05C, 10B and 10I and new investigator information for 09D and 10I
7/20/90	Submitted new investigator information for protocol 11A
7/31/90	Submitted new protocol 14
8/7/90	Submitted new investigator information for 10E, 10G, 12B and 14
8/16/90	Submitted change to protocols 09B and 10C, new protocol 08C and new investigator information for 10D
8/29/90	Submitted new investigator information for protocols 10G and 11
9/25/90	Submitted new protocol 12C, change in protocols 06A and 10I, and new investigator information for protocols 09C and 10I
9/28/90	Submitted change of company name

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DATE	
10/1/90	Submitted new protocols 15, 16, and 17
10/19/90	Submitted new protocol 19 and change to protocol 10H
11/14/90	Submitted new investigator information for protocol 19 and new clinical supplies label for desflurane which reflects the tradename
11/30/90	Submitted site change for protocol 07A
12/4/90	Submitted change to protocols 12A, 15, and 17
12/6/90	Submitted new protocol 13
2/7/91	Submitted new investigator information for protocols 11B and 13
2/11/91	Submitted new protocol 18, change to protocol 18, and new investigator information for protocol 16
4/16/91	Submitted new investigator information for 07, 07A 09A and 18
5/23/91	Submitted Clinical amendment
5/30/91	Submitted changes to protocols 13 and 17 and new investigator information for protocols 11A, 13, and 19B
6/12/91	Submitted change to protocol 08C and new investigator information for protocol 08C
6/21/91	Submitted new protocol 21 and new investigator information for protocol 13
6/25/91	Submitted change of corporate address
7/16/91	Response to FDA request for information re. inclusion criteria for enrollment of women in protocols 08C, 13, and 21
7/22/91	Submitted Pharm/Tox Information Amendment
7/29/91	Submitted change to protocol 17 (Amendment #4) and added investigators to protocol 13
8/9/91	Submitted new protocol 20
8/14/91	Submitted new protocol 22, new investigators to protocols 11C, and 21
8/22/91	Submitted new protocol 12D and Amendment #1 to protocol 12D

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DATE	
9/9/91	Submitted investigator to protocol 21 and changes to protocol 18 (Amendments #2 and #3)
11/12/91	Submitted new protocol 23 and change to protocol 21 (amendment #1)
11/21/91	Submitted annual report for the time period 11/89-11/90
11/26/91	Submitted new protocol 24 and change to protocol 17 (amendment #5)
12/12/91	Received copy of FD 483 issued to one study site
1/2/92	Submitted change to protocol 12D (Amendments #2 and #3)
1/14/92	Submitted protocol amendment adding new investigator to protocol 13 and changes to protocols 08A (amendment 4), 08C (amendment 3), 20 (amendment 1), 22 (amendments 1 & 2), and 23 (amendment 1)
2/12/92	Submitted investigators to protocol 13 and new subinvestigator to protocol 13
2/18/92	Submitted clinical information amendment CMC information amendment
2/18/92	Received a copy of general correspondence between FDA Division of Scientific Investigations clinical investigator)
3/2/92	Received notification from FDA's Division of Scientific Investigations of several significant deficiencies noted for protocol 09A at one study site
3/6/92	Submitted response to FDA Division of Scientific Investigations
3/23/92	General correspondence to FDA Division of Scientific Investigations re. monitoring SOPs
3/26/92	Received general correspondence from FDA Division of Scientific Investigations
4/6/92	Submitted protocol amendment adding investigator to protocol 13, investigator to protocol 21, amendment #1 to protocol 24, and new protocol 26; and clinical information amendment changing subinvestigators for protocols 12D and 20
4/13/92	Received copy of general correspondence re. the inspection of study site
7/10/92	Submitted protocol and clinical information amendments for new protocol 27, new investigator for protocol 13, amendment #2 to protocol 13, additional study site for protocol 21, amendments #2 and #3 to protocol 23, and amendment #1 and new subinvestigator to protocol 26

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DATE	
8/18/92	Clinical information and protocol amendments adding new subinvestigator to study 26, new investigators to studies 13 and 27
9/22/92	Protocol amendment changing protocol 27 (amendment #2) and adding new investigators/sites to protocol 13
10/1/92	CMC amendment and clinical amendment adding subinvestigator to study 13, amendment #3 and new investigators to study 13
10/9/92	Annual report for the time period 12/1/90-11/30/91
10/12/92	CMC information amendment
10/19/92	Clinical information amendment adding subinvestigators and protocol amendment adding investigators/sites to study 13
11/2/92	Protocol amendment for new protocol 25 and new investigators to study 13

SUPRANE™ (desflurane)
NDA 20-118

DATE	
9/27/90	Submitted CMC and Pharm/Tox presubmission to the NDA
9/27/90	Received NDA presubmission cover letter stamped RECEIVED
1/28/91	Submitted full NDA
1/30/91	Received original NDA cover letter stamped RECEIVED
2/26/91	Received acknowledgement of receipt of full NDA and gave the application date as 1/30/91
3/28/91	Conference call with FDA
4/1/91	Received deficiency letter from FDA
4/2/91	Response to 4/1/91 deficiency
4/2/91	Response to pharmacology questions asked at 3/28/91 conference call
4/3/91	Meeting with FDA
4/11/91	Submitted minutes of 4/3/91 meeting
6/13/91	Submitted response to questions raised at 4/3/91 meeting by FDA
6/26/91	Submitted updated list of published animal pharmacology and clinical articles, copy of pharmacology summary, and list of drug names
6/26/91	Hand-delivered file structure of protocol 09A clinical data
6/28/91	Submitted Safety Update to the NDA
7/10/91	Received fax from FDA CSO with the Chemist's comments and a phone memorandum of her 7/10/91 discussion with Anaquest
7/11/91	Phone conversation with FDA CSO re. date of NDA Day and clarification of inclusion criteria for protocols 08C, 13 and 21
7/25/91	Meeting with FDA re. pharm/tox
8/9/91	Submitted fax of revised minutes for the 7/25/91 pharm/tox review meeting to FDA CSO
8/13/91	Submitted response to the chemistry reviewer's comments of 7/10/91 and enclosed revised Methods Validation and Labeling section in response to request by FDA during recent inspection of Anaquest facility

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DATE	
8/14/91	Phone call from FDA re. pharm/tox summaries and dog metabolism protocol
9/3/91	Received phone call from FDA re. our 8/13/91 response to chemistry reviewer's comment of 7/10/91
9/11/91	Submitted response to FDA reviewing pharmacologist's comments made during 7/25/91 meeting
9/12/91	Submitted response to FDA's peer chemist's comments of 8/22/91 and FDA's follow-up of 9/3/91
9/27/91	Submitted data diskette for protocol 05A
10/22/91	Submitted requested statistical information for protocols 05A(1) and (2) and 05B to FDA
11/18/91	Submitted response to 10/23/91 and 11/7/91 FDA requests for new tables for study 07
2/5/92	General correspondence to FDA re. Anaquest's validation plan
2/26/92	Meeting at FDA re. CMC section status, vaporizer, pharmacology and PK review, bibliography, NDA Day, safety update, package insert, and clinical program plan
3/5/92	Meeting with FDA re. container-closure system
3/10/92	Meeting with FDA on minor modifications study summaries
3/11/92	Submitted revised clinical study summary listings per FDA request
3/23/92	Submitted CMC amendment
3/26/92	Submitted response to FDA request for a list of study reports
4/6/92	Meeting with FDA on study summaries for 05A(1) and 10C and the Table of Investigations as well as hand-delivered to FDA 2 computer disks containing the Table of Investigations
4/16/92	Submission to NDA: Correspondence log and copies of all correspondence from the time period 2/26/92 through 4/10/92
4/17/92	Submission to NDA: PDES Master Bibliography, line summary (sorted by author), copies of all articles listed in the bibliography, and a Microsoft Word for Macintosh computer disk containing the master bibliography

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DATE	
4/21/92	Meeting at FDA
4/24/92	Submission to NDA: Response to the Center for Devices and Radiological Health on the 510(k) for the vaporizer as requested by the CSO
5/1/92	Submission to NDA: Latest draft package insert in hard copy and on computer disk
5/8/92	Meeting between Anaquest and FDA: Re. consultant/reviewers, summaries for 11, 08A(1), 12B(2), 06, and 15, labeling outline, safety update, NDA overview/quick reference guide and NDA Day package Table of Contents
5/12/92	Submission to NDA: First update to the PDES Master Bibliography
5/19/92	Submission to NDA: Responses to FDA's comments and data analysis recommendations for studies 07, 07A, 09A, 09B, and 09C
5/21/92	Meeting between Anaquest and FDA: Re. NDA Day planning, package insert, safety update, summaries for 03, 04, 10I, 11, 10 series, 12B(2), 15, 07 and 08A, and the updated computer database
5/21/92	General correspondence from Anaquest to FDA: Response to comments on studies 07, 07A, 09A, 09B, and 09C and enclosing draft prototype summary for study 07
5/21/92	General correspondence from FDA to Anaquest: Brief note from the Philadelphia District Office re. status of methods validation
6/3/92	Meeting between Anaquest and FDA: Re. timelines for remaining summaries, draft summaries for 15 (incl. figures), 08A(1), 11, and 12B(2), package insert, and adverse event report
6/8/92	Submission to NDA: Two final preclinical mouse study reports and an update for the carcinogenesis section of package insert to reflect the addition of these two study reports
6/9/92	Submission to NDA Final clinical summaries for studies 05A(1), 05A(2), 05B, 05C, 05D

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DATE	
6/9/92	Submission to NDA: Final clinical summaries for the studies 10A(1), 10A(2), 10B, 10C, 10D, 10E, 10F, 10G, 10H, 10J, 10K(UK), 10K(FR)
6/10/92	Submission to NDA: Final clinical summaries for studies 01, 02, 06A, 06B, 06C, 12A, 12C
6/11/92	Submission to NDA: Final clinical summaries for studies 08A(1), 08A(2), 08B, 08C
6/12/92	Submission to NDA: Final clinical summaries for studies 03, 04, 10I
6/15/92	Submission to NDA: Final clinical summaries for studies 15, 16, 17
6/16/92	Submission to NDA: Final clinical summaries for studies 11, substudy 11, 19, 12B(1), 12B(2), 07, 07A, 09A, 09B, 09C 09D, and 14
6/19/92	General Correspondence from Anaquest to FDA: Copies of all clinical summaries in preparation for the 6/23/92 meeting at FDA
6/23/92	Meeting between Anaquest and FDA: Re. clinical trials section of the package insert, demographics for multicenter studies, figures for 10A(1) and (2), reanalysis of 09A, revisions to study summaries, and NDA Day preparation
6/25/92	Submission to NDA: Second update to the PDES Master Bibliography and line summary
6/26/92	Submission to NDA: Revised package insert, study summaries 15, 17 08A(1), 08A(2), and 08C
6/29/92	Submission to NDA: Response to FDA request for entire PDES Master Bibliography, line summary, and clinical summary 04 in hard copy and on IBM Microsoft Word disk
7/1/92	Submission to NDA: Response to request for information on studies 15 and 17
7/9/92	Submission to NDA: Third update to the PDES Master Bibliography and line summary
7/21/92	Submission to NDA: Fourth update to the PDES Master Bibliography and line summary

SUPRANE™ (desflurane)
NDA 20-118

DATE	
7/28/92	Submission to NDA: Response to FDA request for an Integrated Safety Summary Update
7/28/92	Submission to NDA: Correspondence log and copies of all telephone/meeting minutes not previously submitted from the time period 6/17/92-7/24/92
7/29/92	Submission to NDA: Response to FDA request for final clinical study summaries with a list of all changes and their origin
8/3/92	Submission to NDA: Response to FDA comments re. the storage statement and the chemical name and structure in description section of the package insert
8/4/92	Submission to NDA: Response to FDA request for study summary 04 on IBM compatible disk and in hard copy
8/4/92	Meeting at FDA: Discussion on expiration dating and storage conditions
8/5/92	Submission to NDA: Response to FDA request for 5 bound copies of articles from the Master Bibliography and a disk (IBM format) of study summary 04
8/7/92	Submission to NDA: Fifth update to the PDES Master Bibliography and line summary
8/7/92	Submission to NDA: Response to FDA request for final revised hard copies of study summaries for incorporation in the NDA pack and a list of all changes made
8/11/92	Submission to NDA: Appendices to the NDA pack and a computer disk containing first pages of the clinical summaries
8/14/92	Submission to NDA: Advertising/promotion pieces
8/17/92	General Correspondence from FDA to Anaquest: NDA Day Package/FDA Review including package insert
8/20/92	Submission to NDA: Proposed promotional launch materials

SUPRANE™ (desflurane)
NDA 20-118

DATE	
8/21/92	Submission to NDA: Response to request for updated stability data and minutes of 8/4/92 meeting at FDA
8/21/92	Submission to NDA: Response to FDA request for revised specifications and directions for testing drug substance, drug product, and reference standard (revised analytical methods)
8/28/92	Submission to NDA: Additional information clarifying statistical plots of stability data
8/31/92	NDA Day
9/1/92	NDA Day (continued)
9/1/92	Meeting between Anaquest and FDA: AE section of the package insert as discussed at FDA
9/10/92	Submission to NDA: Advertising/promotion
9/18/92	Received from FDA the original APPROVAL LETTER and final package insert

v. The patent was issued after the enactment date of 35 U.S.C. §156, September 24, 1984, and the IND and NDA for the Product were filed subsequent to that date. Therefore, the term of the patent may be extended for up to five years under 35 U.S.C. §156(g)(4)(B).

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to this Application for Extension.

(14) Please find attached a money order in the amount of $1000.00 which is the fee for receiving and acting upon this Application for Extension.

(15) Please find the approved labeling information used for the Product as Attachment 3.

(16) Telephone contacts and correspondence relating to this Application for Extension are to be directed to:

Hollis G. Schoepke, Ph.D.
Senior Vice President of Research and Development
Anaquest, Inc.
110 Allen Road
P.O. Box 804
Liberty Corner, New Jersey 07938
(908) 604-7607

(12) It is the opinion of the Applicant that U.S. Patent No. 4,762,856 is eligible for extension because (a) the patent claims a method of using the Product; (b) the term of the patent has never been extended; (c) this Application is submitted in compliance with all requirements of 35 U.S.C. §156(d) the Product has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) and by the Secretary of Health and Human Services before its commerical marketing or use; (e) the Applicant has received permission from FDA for commerical marketing and use of the Product; (f) this Application is submitted within the sixty day period after the Product first received permission for commercial marketing and use; (g) the term of the patent has not expired before submission of this Application; and (h) no other patent has been extended for the same regulatory review period for this Product.

The Applicant further states that U.S. Patent No. 4,762,856 is entitled to an extension of 406 days for the following reasons:

i. All of the regulatory review period of 1,368 days (i.e., December 21, 1988 through September 18, 1992) occurred after the date the patent was issued, August 9, 1988. 37 C.F.R. §1.775(d)(1)(i).

ii. The Applicant pursued the approval of the Product during the regulatory period with "due diligence", as defined by 35 U.S.C.§156(d)(3). 37 C.F.R §1.775(d)(1)(ii).

iii. The 1,368 day regulatory review is reduced by 385 days, which is half of the IND period (770 days), to yield a total of 983 days. 37 C.F.R. §1.775(d)(1)(iii).

iv. Adding 983 days to the term of the patent remaining after the date of NDA approval of the Product, September 18, 1992, would result in a patent term that would be more than 14 years after the date of NDA approval. 37 C.F.R. §1.775(d)(4). Therefore, the maximum period of patent term extension may be only until September 18, 2006, or 14 years after the date of NDA approval. This means that the patent term may be extended by 406 days.

(17) A duplicate copy of all papers, certified as such, is also attached to this Application as Attachment 4.

(18) A Declaration of Authority confirming authority for Dr. Hollis Schoepke to sign this request for extension is included as Attachment 5.

Anaquest, Inc.

By: _____

Hollis G. Schoepke, Ph.D.
Senior Vice President
Research and Development
Anaquest, Inc.

Date: 13 Nov 92

ATTACHMENT 1

PATENT ASSIGNMENT INFORMATION

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

5/88

TO: THE BOC GROUP, INC.
PATENT, TRADEMARK & LICENSING DEPART.
100 MOUNTAIN AVENUE
MURRAY HILL, NEW PROVIDENCE, NJ 07974

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 TERRELL, ROSS C. DOC DATE: 01/28/87

RECORDATION DATE: 02/02/87 NUMBER OF PAGES 001 REEL/FRAME 4666/0467

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 BOC, INC., 85 CHESTNUT RIDGE RD., MONTVALE N.J. 07645 A C ORP. OF DE.

SERIAL NUMBER 7-010106 FILING DATE 02/02/87
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: ANESTHETIC COMPOSITION AND METHOD OF USING THE SAM E

INVENTOR: 001 TERRELL, ROSS C.

THE BOC GROUP

ASSIGNMENT

WHEREAS, I, ROSS CLARK TERRELL a citizen of the United States, residing at 615 Goodmans Crossing, Clark, New Jersey 07066 have invented certain new and useful improvements in "ANESTHETIC COMPOSITION AND METHOD OF USING THE SAME" for which I have executed an application for Letters Patent of the United States, of even date herewith; and January 28, 1987

WHEREAS, BOC, Inc., a Delaware Corporation having an office at 85 Chestnut Ridge Road, Montvale, New Jersey 07645, is desirous of obtaining the entire right, title and interest in, to and under the said improvements and the said application: "ANESTHETIC COMPOSITION AND METHOD OF USING THE SAME"

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) to me in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, I, the said Ross Clark Terrell have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said BOC, Inc., its successors, legal representatives and assigns, the entire right, title and interest in, to and under the said improvements, and the said application and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and I hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said BOC, Inc., its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND I HEREBY covenant that I have full right to convey the entire interest herein assigned, and that I have not executed, and will not execute, any agreement in conflict herewith.

AND I HEREBY further covenant and agree that I will communicate to the said BOC, Inc., its successors, legal representatives and assigns, any facts known to me respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths, and generally do everything possible to aid the said BOC, Inc., its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 28th day of January, 1987

Ross C. Terrell L. S.

State of NEW JERSEY }
County of UNION } ss.:

On this 28 day of January 1987, before me, a Notary Public in and for the State and County aforesaid, personally appeared ROSS CLARK TERRELL to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he/she acknowledged the same to be his/her free act and deed.

Notary Public
MY COMMISSION EXPIRES
JUNE 3, 1991

B 737 - 3/84

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DOCKET: RHS
REC'D
MAR 11 1991
PAT. DEPT.
INFO:

TO: THE BOC GROUP, INC.
100 MOUNTAIN AVENUE
PATENT DEPT.
MURRAY HILL, NEW PROVIDENCE, NJ 07974

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 BOC, INC. DOC DATE: 12/10/90

RECORDATION DATE: 12/17/90 NUMBER OF PAGES 002 REEL/FRAME 5544/0575

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 ANAQUEST, INC., 575 MOUNTAIN AVENUE, MURRAY HILL, NEW PROVIDENCE, NJ 07974

SERIAL NUMBER 7-010106 FILING DATE 02/02/87
PATENT NUMBER 4,762,856 ISSUE DATE 08/09/88

ASSIGNMENT OF U.S. PATENT

WHEREAS, BOC, Inc., having its principal office and place of business at 575 Mountain Avenue, Murray Hill, New Providence, New Jersey 07974 (hereafter "Assignor") is the owner of U.S. Patent No. 4,762,856, issued August 9, 1988 by virtue of an Assignment recorded in the U.S. Patent and Trademark Office on February 2, 1987, Reel 4666, Frame 467; and

WHEREAS, Anaquest, Inc., having its office and principal place of business at 575 Mountain Avenue, Murray Hill, New Providence, New Jersey 07974, (hereafter "Assignee") is desirous of acquiring said patent.

NOW, THEREFORE, TO WHOM IT MAY CONCERN, be it known that for a good and valuable consideration, the receipt of which is hereby acknowledged by said Assignor, said Assignor by these presents does hereby sell, assign, and transfer to Assignee, its successors and assigns, as of October 26, 1990, its entire right, title, and interest in and to said patent, and in and to any and all reissues or extension thereof, and all Letters Patent corresponding thereto in any country or countries foreign to the United States and all extensions, renewals and reissues thereof.

RECORDED
PATENT AND TRADEMARK OFFICE
DEC 17 1990

For: BOC, Inc.

By: Debajyoti Chatterji
Debajoyoti Chatterji
Managing Director,
Technology

State of NEW JERSEY)
) ss.
County of Union)

On this the 10 th day of December, 1990, before me, a Notary Public within and for said County, personally appeared Debajoyoti Chatterji, to me personally known, who, being by me duly sworn on oath did say that he is the Managing Director, Technology of said corporation, and that said instrument was signed and sealed in behalf of said corporation by authority of its Board of Directors and said Debajoyota Chatterji acknowledged said instrument to be the free act and deed of said corporation.

Marie Maluso
Notary Public

[Seal]

MARIE MALUSO
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION EXPIRES MARCH 17, 1993

REEL5514 FRAME576

ATTACHMENT 2

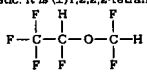
COPY OF PATENT

Suprane™ (desflurane)

Volatile Liquid for Inhalation

DESCRIPTION

SUPRANE™ (desflurane), a nonflammable liquid administered via vaporizer, is a general inhalation anesthetic. It is (±)1,2,2,2-tetrafluoroethyl difluoromethyl ether:



Some physical constants are:

Molecular weight	168.04
Specific gravity (at 15°C/4°C)	1.4672
Vapor pressure in mm Hg	669 mm Hg @ 20°C 731 mm Hg @ 22°C 757 mm Hg @ 22.8°C (boiling point; 1 atm) 764 mmHg @ 23°C 798 mmHg @ 24°C 869 mmHg @ 26°C

Partition coefficients at 37°C:

Blood/Gas	0.424
Olive Oil/Gas	18.7
Brain/Gas	0.54

Mean Component/Gas Partition Coefficients:

Polypropylene (Y piece)	6.7
Polyethylene (circuit tube)	16.2
Latex rubber (bag)	19.3
Latex rubber (bellows)	10.4
Polyvinylchloride (endotracheal tube)	34.7

Desflurane is nonflammable as defined by the requirements of International Electrotechnical Commission 601-2-13.

Desflurane is a colorless, volatile liquid below 22.8°C. Data indicate that desflurane is stable when stored under normal room lighting conditions according to instructions.

Desflurane is chemically stable. The only known degradation reaction is through prolonged direct contact with soda lime producing low levels of fluoroform (CHF_3). The amount of CHF_3 obtained is similar to that produced with MAC-equivalent doses of isoflurane. No discernible degradation occurs in the presence of strong acids.

Desflurane does not corrode stainless steel, brass, aluminum, anodized aluminum, nickel plated brass, copper, or beryllium.

CLINICAL PHARMACOLOGY

SUPRANE™ (desflurane) is a volatile liquid inhalation anesthetic minimally biotransformed in the liver in humans. Less than 0.02% of the SUPRANE™ (desflurane) absorbed can be recovered as urinary metabolites (compared to 0.2% for isoflurane).

Minimum alveolar concentration (MAC) of desflurane in oxygen for a 25 year-old adult is 7.3%. The MAC of SUPRANE™ (desflurane) decreases with increasing age and with addition of depressants such as opioids or benzodiazepines. (See DOSAGE AND ADMINISTRATION for details).

Pharmacokinetics

Due to the volatile nature of desflurane in plasma samples, the washin-washout profile of desflurane was used as a surrogate of plasma pharmacokinetics. Eight healthy male volunteers first breathed 70% N_2O/30% O_2 for 30 minutes and then a mixture of SUPRANE™ (desflurane) 2.0%, isoflurane 0.4%, and halothane 0.2% for another 30 minutes. During this time, inspired and end-tidal concentrations (F_I and F_A) were measured. The F_A/F_I (washin) value at 30 minutes for desflurane was 0.91, compared to 1.00 for N_2O, 0.74 for isoflurane, and 0.58 for halothane (See Figure 1). The washin rates for halothane and isoflurane were similar to literature values. The washin was faster for desflurane than for isoflurane and halothane at all time points. The F_A/F_{AO} (washout) value at 5 minutes was 0.12 for desflurane, 0.22 for isoflurane, and 0.25 for halothane (See Figure 2). The washout for SUPRANE™ (desflurane) was more rapid than that for isoflurane and halothane at all elimination time points. By 5 days, the F_A/F_{AO} for desflurane is 1/20th of that for halothane or isoflurane.

Figure 1.
Desflurane Washin
Mean ± SD
8 Normal Male Volunteers

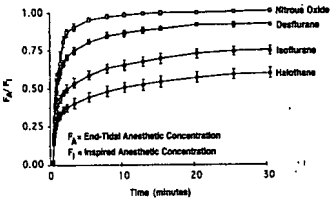
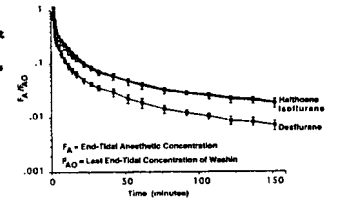


Figure 2.
Desflurane Washout
Mean ± SD
8 Normal Male Volunteers



Pharmacodynamics

Changes in the clinical effects of SUPRANE™ (desflurane) rapidly follow changes in the inspired concentration. The duration of anesthesia and selected recovery measures for SUPRANE™ (desflurane) are given in the following tables:

In 178 female outpatients undergoing laparoscopy, premedicated with fentanyl (1.5-2.0 µg/kg), anesthesia was initiated with propofol 2.5 mg/kg, desflurane/N_2O 60% in O_2 or desflurane/O_2 alone. Anesthesia was maintained with either propofol 1.5-9.0 mg/kg/hr, desflurane 2.6-8.4% in N_2O 60% in O_2, or desflurane 3.1-8.9% in O_2.

EMERGENCE AND RECOVERY AFTER OUTPATIENT LAPAROSCOPY
178 FEMALES, AGES 20-47
TIMES IN MINUTES: MEAN ± SD (RANGE)

Induction: Maintenance: Number of Pts:	Propofol Propofol/N_2O N = 48	Propofol Desflurane/N_2O N = 44	Desflurane/N_2O Desflurane/N_2O N = 43	Desflurane/O_2 Desflurane/O_2 N = 43
Median age	30 (20-43)	26 (21-47)	29 (21-42)	30 (20-40)
Anesthetic Time	49 ± 53 (8-336)	45 ± 35 (11-178)	44 ± 29 (14-149)	41 ± 26 (19-126)
Time to open eyes	7 ± 3 (2-19)	5 ± 2* (2-10)	5 ± 2* (2-12)	4 ± 2* (1-11)

SUPRANE™ (desflurane) was studied in twelve volunteers receiving no other drugs. Hemodynamic effects during controlled ventilation (Pa_{CO_2} 38mm Hg) were:

HEMODYNAMIC EFFECTS OF DESFLURANE DURING CONTROLLED VENTILATION
12 MALE VOLUNTEERS, AGES 16-26
MEAN ± SD (RANGE)

Total MAC Equivalent	End-Tidal % Des/O_2	End-Tidal % Des/%N_2O	Heart Rate (beats/min) O_2	Heart Rate (beats/min) N_2O	Mean Arterial Pressure (mmHg) O_2	Mean Arterial Pressure (mmHg) N_2O	Cardiac Index (L/min/m2) O_2	Cardiac Index (L/min/m2) N_2O
0	0% / 21%	0% / 0%	69 ± 4 (63-76)	70 ± 6 (62-85)	85 ± 9 (74-102)	85 ± 9 (74-102)	3.7 ± 0.4 (3.0-4.2)	3.7 ± 0.4 (3.0-4.2)
0.8	6% / 94%	3% / 60%	73 ± 5 (67-80)	77 ± 8 (67-97)	61 ± 5* (55-70)	69 ± 5* (62-80)	3.2 ± 0.5 (2.6-4.0)	3.3 ± 0.5 (2.6-4.1)
1.2	9% / 91%	6% / 60%	80 ± 5* (72-84)	77 ± 7 (67-90)	59 ± 8* (44-71)	63 ± 8* (47-74)	3.4 ± 0.5 (2.6-4.1)	3.1 ± 0.4* (2.6-3.8)
1.7	12% / 88%	9% / 60%	94 ± 14* (78-109)	79 ± 9 (61-91)	51 ±12* (31-66)	59 ± 6* (46-68)	3.5 ± 0.9 (1.7-4.7)	3.0 ± 0.4* (2.4-3.6)

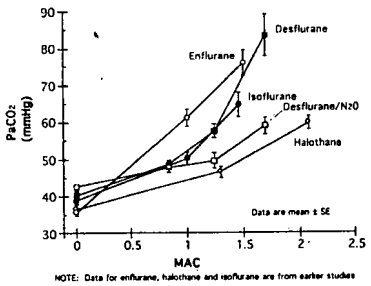
*Differences were statistically significant (p<0.05) compared to awake values, Newman-Keul's method of multiple comparison.

When the same volunteers breathed spontaneously during desflurane anesthesia, systemic vascular resistance and mean arterial blood pressure decreased; cardiac index, heart rate, stroke volume, and central venous pressure (CVP) increased compared to values when the volunteers were conscious. Cardiac index, stroke volume, and CVP were greater during spontaneous ventilation than during controlled ventilation.

During spontaneous ventilation in the same volunteers, increasing the concentration of SUPRANE™ (desflurane) from 3% to 12% decreased tidal volume and increased arterial carbon dioxide tension and respiratory rate. The combination of N_2O 60% with a given concentration of desflurane gave results similar to those with desflurane alone. Respiratory depression produced by desflurane is similar to that produced by other potent inhalation agents.

The use of desflurane concentrations higher than 1.5 MAC may produce apnea.

Figure 3. $PaCO_2$ During Spontaneous Ventilation in Unstimulated Volunteers



NOTE: Data for enflurane, halothane and isoflurane are from earlier studies

CLINICAL TRIALS

SUPRANE™ (desflurane) was evaluated in 1,843 patients including ambulatory (N=1,061), cardiovascular (N=277), geriatric (N=103), neurosurgical (N=40), and pediatric (N=235) patients. Clinical experience with these patients and with 1,087 control patients in these studies not receiving desflurane are described below. Although desflurane can be used in adults for the inhalation induction of anesthesia via mask, it produces a high incidence of respiratory irritation (coughing, breathholding, apnea, increased secretions, laryngospasm). For incidence, see ADVERSE REACTIONS. Oxyhemoglobin saturation below 90% occurred in 6% of patients (from pooled data, N = 370 adults).

Ambulatory Surgery

SUPRANE™ (desflurane) plus N_2O was compared to isoflurane plus N_2O in multicenter studies (21 sites) of 792 ASA physical status I, II, or III patients aged 18-76 years (median 32).

Induction: Anesthetic induction begun with thiopental and continued with desflurane was associated with a 7% incidence of oxyhemoglobin saturation of 90% or less (from pooled data, N = 307) compared with 5% in patients in whom anesthesia was induced with thiopental and isoflurane (from pooled data, N = 152).

Maintenance & Recovery: SUPRANE™ (desflurane) with or without N_2O or other anesthetics was generally well tolerated. There were no differences between desflurane and the other anesthetics studied in the times that patients were judged fit for discharge.

In one outpatient study, patients received a standardized anesthetic consisting of thiopental 4.2-4.4 mg/kg, fentanyl 3.5-4.0 µg/kg, vecuronium 0.05-0.07 mg/kg, and N_2O 60% in oxygen with either desflurane 3% or isoflurane 0.6%. Emergence times were significantly different; but times to sit up and discharge were not different (see Table).

RECOVERY PROFILES AFTER DESFLURANE 3% IN N_2O 60%
VS ISOFLURANE 0.6% IN N_2O 60% IN OUTPATIENTS
16 MALES, 22 FEMALES, AGES 20-65
MEAN ± SD

	Isoflurane	Desflurane
Number	21	17
Anesthetic time (min)	127 ± 80	98 ± 55
Recovery time to:		
Follow commands (min)	11.1 ± 7.9	6.5 ± 2.3*
Sit up (min)	113 ± 27	95 ± 56
Fit for discharge (min)	231 ± 40	207 ± 54

* Difference was statistically significant from the isoflurane group (p < 0.05), unadjusted for multiple comparisons.

Cardiovascular Surgery

Desflurane was compared to isoflurane, sufentanil or fentanyl for the anesthetic management of coronary artery bypass graft (CABG), abdominal aortic aneurysm, peripheral vascular and carotid endarterectomy surgery in 7 studies at 15 centers involving a total of 558 patients. In all patients except the desflurane vs sufentanil study, the volatile anesthetics were supplemented with intravenous opioids, usually fentanyl. Blood pressure and heart rate were controlled by changes in concentration of the volatile anesthetics or opioids and cardiovascular drugs if necessary. Oxygen (100%) was the carrier gas in 253 of 277 desflurane cases (24 of 277 received N_2O/O_2).

CARDIOVASCULAR PATIENTS BY AGENT AND TYPE OF SURGERY
418 MALES, 140 FEMALES, AGES 27-87 (MEDIAN 64)

Type of Surgery	13 Centers Isoflurane	 Desflurane	1 Center Sufentanil	 Desflurane	1 Center Fentanyl	 Desflurane

ATTACHMENT 3

APPROVED PRODUCT LABELING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,762,586 Attn: Box Patent Ext

Inventor: Ross C. Terrell, Clark,NJ

Issued Date: August 9, 1988

Original Assignee: BOC, Inc., Montvale, NJ

Current Assignee: Anaquest, Inc., Liberty Corner, NJ

CERTIFICATION

The undersigned hereby certifies that the attached document is a duplicate of the Request for Extension of U.S. Patent No. 4,762,856 which is concurrently submitted.

Anaquest, Inc.

By: _____

Hollis G. Schoepke, Ph.D.
Senior Vice President
Research and Development
(908) 604-7607

Date: 13 Nov 92

ATTACHMENT 4

DUPLICATE COPY

ATTACHMENT 5

DECLARATION OF AUTHORITY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.:	4,762,586
Issued Date:	August 9, 1988
Inventor	Ross C. Terrell, Clark, N.J.
Original Assignee:	BOC, Inc., Montvale, N.J.
Current Assignee:	Anaquest, Inc., Liberty Corner, NJ
For:	

DECLARATION OF

1. I am Hollis Schoepke, Ph.D.

2. This declaration concerns the Application for Extension of Patent Term dated for the extension of U.S. Patent No. 4762856 submitted by Ross C. Terrell, Clark, N.J.

3. by signing this declaration, I affirm that:

   a. I am an agent of the corporate owner authorized to obligate the corporation;

   b. I have reviewed and understand the contents of the afore said application being submitted pursuant to 37 C.F.R. §1.740;

   c. I believe the said patent is subject to extension pursuant to 37 C.F.R. §1.710;

d. I believe an extension of the length claimed is fully justified under 35 U.S.C. §156 and applicable regulations;

e. I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720; and

f. I have been given the authority by the owner of record to execute the application for Extension of Patent Term and this declaration on its behalf.

By: _____

Hollis G. Schoepke, Ph.D.
Senior Vice President
Research and Development
Anaquest, Inc.
(908) 604-7607

Date: 13 Nov 92